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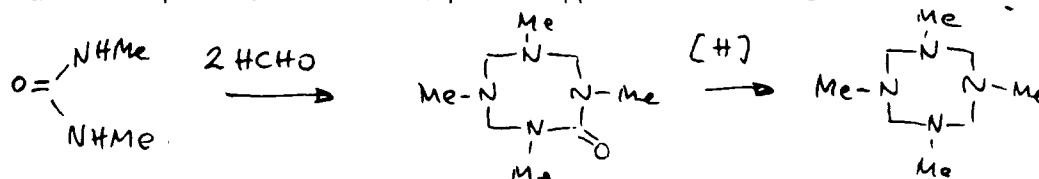
Ref.: Contract No. DAJA 45-85-C-0016
"New Synthetic Approaches to TAT"

Seventh Interim Report (Item 0008)

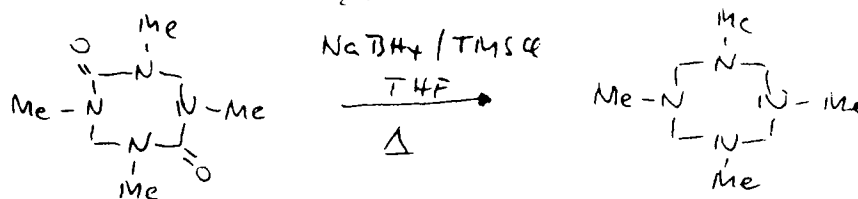
In continuation of our current research project we are trying to obtain new synthetic approaches to the TAT molecule along the following three pathways (cf. previous Interim Reports):

- (a) ring synthetic methods from small molecules
- (b) selective bridge removal in DAPT
- (c) template catalyzed cyclomerization of methyleneimines

A fourth pathway ("ureas as starting materials") mentioned firstly in the 6th Interim Report, namely to perform simple α -ureidoalkylation (cf. H. Petersen, *Synthesis* 1973, 243) to obtain dioxotetrazocanes, or to start with N,N'-dimethylurea and formaldehyde (according Kadowaki, *Bull.Chem.Soc.Japan* 11, 248 (1936)), has been further developed to a novel and independent approach to the tetrazocane molecules.



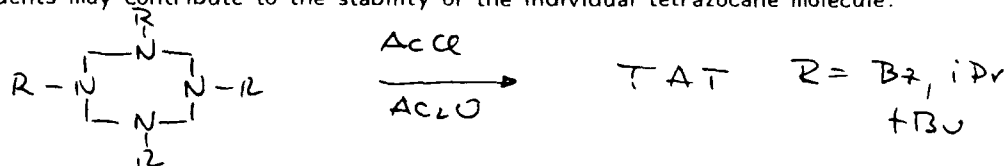
This effort was made possible by a novel mild, but energetic reduction agent, found earlier by another group in our Department (patent pending). This reagent consists of a combination of $\text{LiBH}_4/\text{Me}_3\text{SiCl}$ proceeding by an attack of the Lewis acid Me_3Si^+ while B_2H_6 seems to be the powerful but mild reducing agent. The reduction couple $\text{NaBH}_4/\text{Me}_3\text{SiCl}$ has a comparable potency, and was firstly applied to the cyclic ureide model compound:



Although, the resulting 1,3,5,7-tetramethyltetrazocane proved to be a labile compound (traces of moisture lead to a rapid decomposition), some primary spectral measurements could be carried out: in the $^1\text{H-NMR}$ only two characteristic signals have been detected in the typical N-Me and -N-CH₂-N- ranges; in the IR the C=O groups have disappeared, and a high resolution MS is on the way (incl. C-H-N determination of the parent peak).

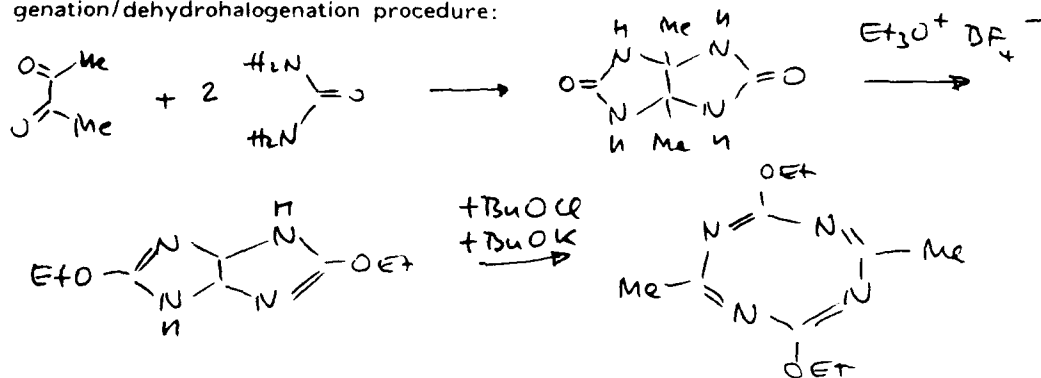
This tetrazocane synthesis represents in a kind of breakthrough a rather simple approach from easily accessible ureas and formaldehyde in few steps and with a selective reduction of the intermediary stable dioxotetrazocane.

Now we are trying to transfer this sequence consequently to dibenzyl-, diisopropyl- or di-tert.butyl-ureas, hoping that these more bulky and easily exchangeable substituents may contribute to the stability of the individual tetrazocane molecule:



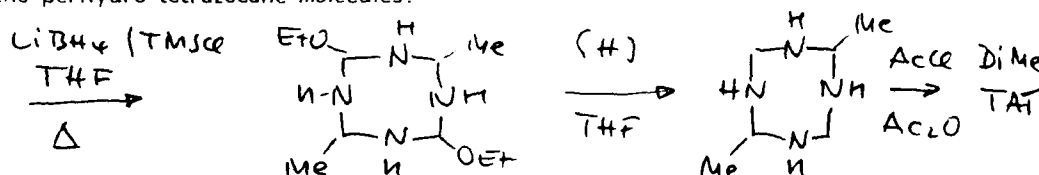
Another promising approach to TAT is under investigation now, which we call the "electrocyclic approach":

Following a procedure shown first in 1983 by R. Gompper and M.L. Schwarzensteiner (Angew. Chem. 95, 553 (1983); Angew. Chem. Int. Ed. Engl. 22, 543 (1983); Angew. Chem. Suppl. 1983, 812), we start from 1,5-dimethyl-glycouril, easily accessible from urea and diacetyl; this is smoothly O-alkylated by Meerweins reagent, and subsequently oxidized by tBuOCl/tBuOK and thus ringenlarged in a typical halogenation/dehydrohalogenation procedure:



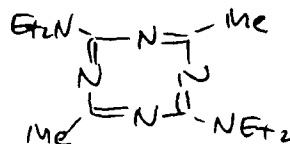
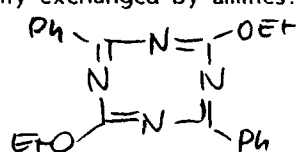
To our knowledge and experience with analogous systems (cf. R-TAD) the exper-

sive tBuOCl might be exchanged for the cheaper and better to handle NBS. Hydrogenation with the forementioned reagent $\text{LiBH}_4/\text{TMSCl}$ is expected to afford smoothly the perhydro-tetrazocane molecules:

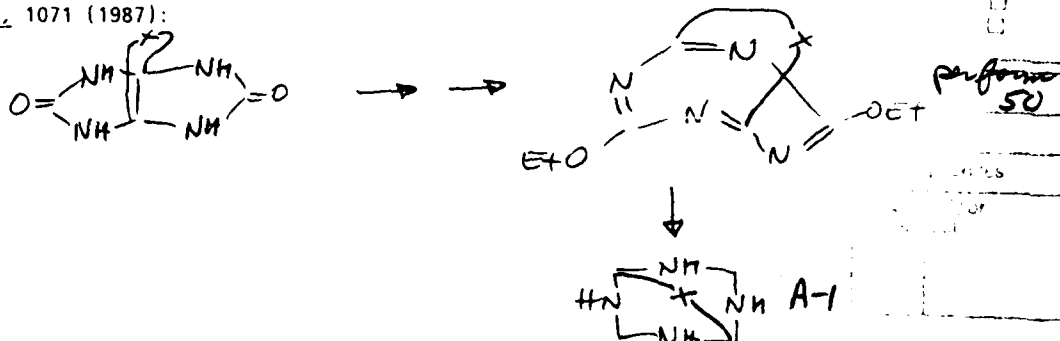


whereby a simultaneous hydrogenolysis of the ethoxy groups seems to be likely. Interception of the intermediate with $\text{AcCl}/\text{Ac}_2\text{O}$ should lead again to dimethyl TAT. By employing glyoxal, the parent ring compound TAT seems to be easily accessible.

This reaction can be extended also to benzile, or the ethoxy groups can be nucleophilically exchanged by amines:



Furthermore, the easy introduction of bridging units employing cyclo-1,2-diketones can offer a considerable stabilization effect (cf. R. Gompper et al., Angew.Chem. 99, 1071 (1987)):



In the literature we have noticed that some peri substituted 2,4,6,8-tetraazabicyclo-[3.3.0]octanes and their N-derivatives have been investigated very recently (cf. M. Koppes, M. Chaykovsky, H.G. Adolph, R. Gilardi, C. George, J.Org.Chem. 52, 1113 (1987)).

In the future, more extended approaches are planned by ring synthetic methods from small molecules and in the presence of novel catalysts with definite cavities; and on this novel research into a "new third dimension" we are currently preparing for submitting an additional application for an one-year-extension of the current Contract No. DAJA 45-85-C-0016.

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 Contractor